ARRANON® (nelarabine) Injection (NDA 21-877) Accelerated Approval Update

Oncology Drugs Advisory Committee

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Presentation Overview

- History of Arranon accelerated approval
- Establishment of post-marketing commitment
- Description of trial
  - Original timelines
  - Current estimate of timelines

Background Information

- Accelerated approval date: October 28, 2005
- Indication: Treatment of patients with T-cell acute lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens
- Orphan designation: August 2004
- Incidence of disease:
  - Estimated 1600 new cases of T-ALL / T-LBL per year U.S.
  - Less than 300 patients with second relapse

Arranon Approval

- COG P9673 (Study PGAA2001):
  - A Phase II monotherapy
  - Children with Refractory T-Cell Malignancies
  - Enrolled 151 subjects over 5 years
    - 39 subjects in target indication
- CALGB19801 (Study PGAA2002):
  - A Phase II monotherapy
  - Adults with Refractory or Relapsed T-Lineage Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma (LBL)
  - Enrolled 39 subjects over 3 years
    - 28 Subjects in target indication

Pivotal Studies: Clinical Efficacy Results

	Study COG P9673 (n = 39)	Study CALGB 19801 (n = 28)
Patient Population	Subjects 21 Years of Age and Younger at Diagnosis With ≥ 2 Prior Inductions	Adult Subjects With ≥ 2 Prior Inductions
CR plus CR*	9/39 (23%)	6/28 (21%)
CR	5/39 (13%)	5/28 (18%)
CR*	4/39 (10%)	1/28 (4%)
CR plus CR* Duration	3.3 to 9.3 weeks	4 to 195+ weeks

[1]CR = complete response (defined as bone marrow blast counts ≥5%, no other evidence of disease, and full recovery of peripheral blood counts) with full hematologic recovery
CR* = complete response without full hematologic recovery
CR plus CR* = total of patients achieving best response in either category

Berg et al, JCO, 2005
DeAngelo et al, Blood, 2007

Arranon Safety Profile

- Arranon was studied in 459 patients in Phase I and Phase II clinical trials
- Common adverse reactions:
  - Adults: fatigue, gastrointestinal disorders, hematologic disorders, respiratory disorders, nervous system disorders, and pyrexia
  - Pediatrics: hematologic disorders, headache, increased transaminase levels, decreased blood potassium, decreased blood albumin, increased blood bilirubin, and vomiting
- **Black Box Warning** for neurologic adverse reactions and administration should be discontinued for AEs of ≥ grade 2

Post-marketing Commitment

- Submit the results of the proposed phase III trial (AALL0434) to be conducted by the Children's Oncology Group to demonstrate nelarabine's clinical benefit

Milestone	Date
Approval	28 Oct 2005
First patient enrolled:	April 2006
End of safety phase:	4Q 2009
Complete Accrual:	4Q 2012
Complete 3-year follow-up:	4Q 2015
Availability of study report:	4Q 2016

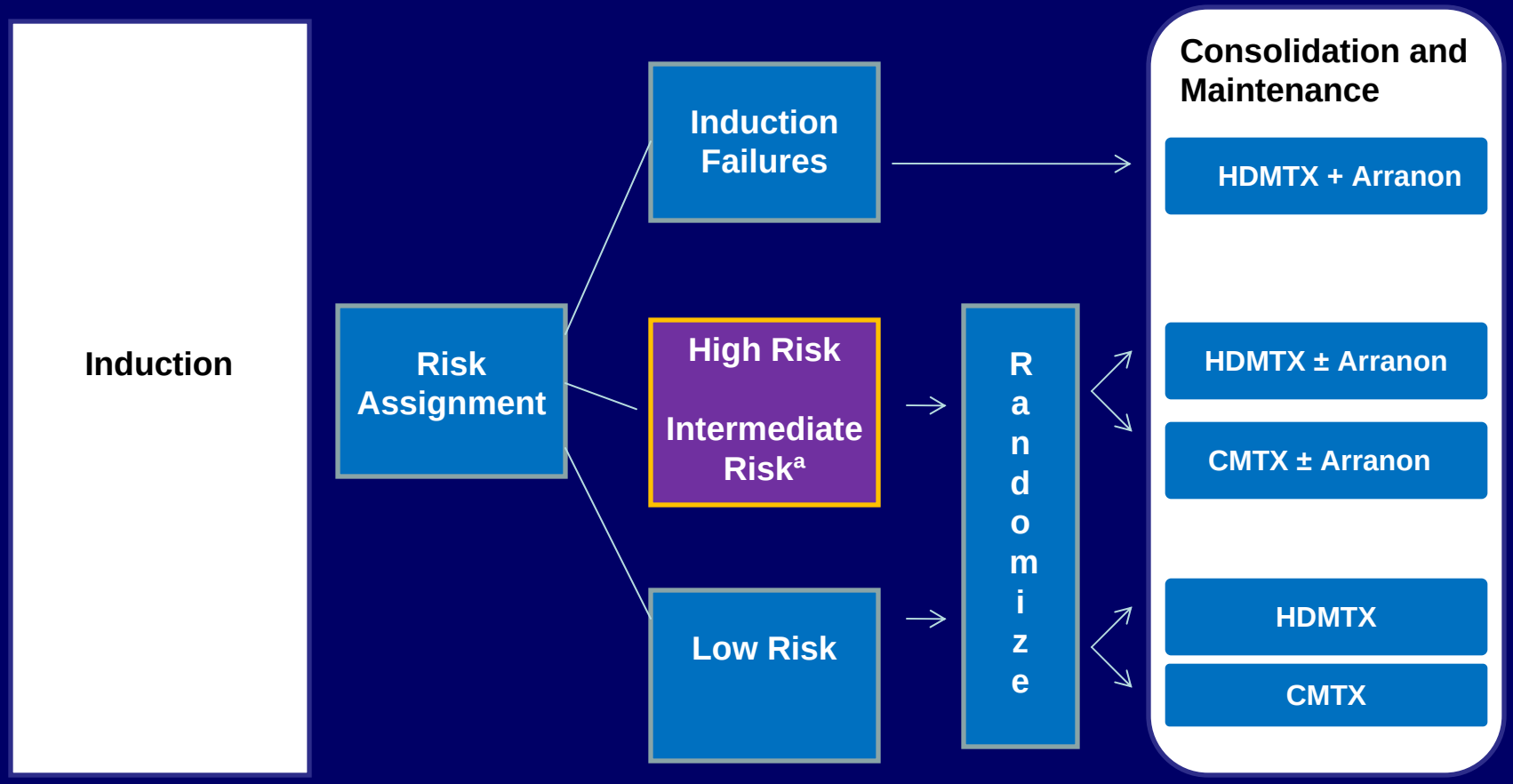
- A Special Protocol Assessment should be submitted prior to initiation of the study

Post-marketing Commitment Study

Study AALL0434

- Intensified Methotrexate, Arranon and Augmented BFM Therapy for Children and Young Adults with Newly Diagnosed T-cell Acute Lymphoblastic Leukemia (ALL) or T-cell Lymphoblastic Lymphoma
- Conducted by COG under NCI IND 52,611
- 2 x 2 factorial design
- Consolidation and maintenance with:
  - High dose methotrexate vs Capizzi methotrexate
  - Arranon vs no addition
- Safety Phase followed by Efficacy Phase
- Co-PIs Drs Stuart Winter and Kim Dunsmore

AALL0434 Study Design



[a]Arranon in Efficacy Phase

Event Free Survival at 4 years

AALL0434 Projected enrollment

- Total N=1380
  - N=1206 randomized to Methotrexate optimization arms
  - N=615 randomized to Arranon benefit assessment arms
    - Est. 240 high-risk and 375 intermediate-risk
- Open to all the COG sites
  - Currently enrolling patients at 168 centers in 6 countries

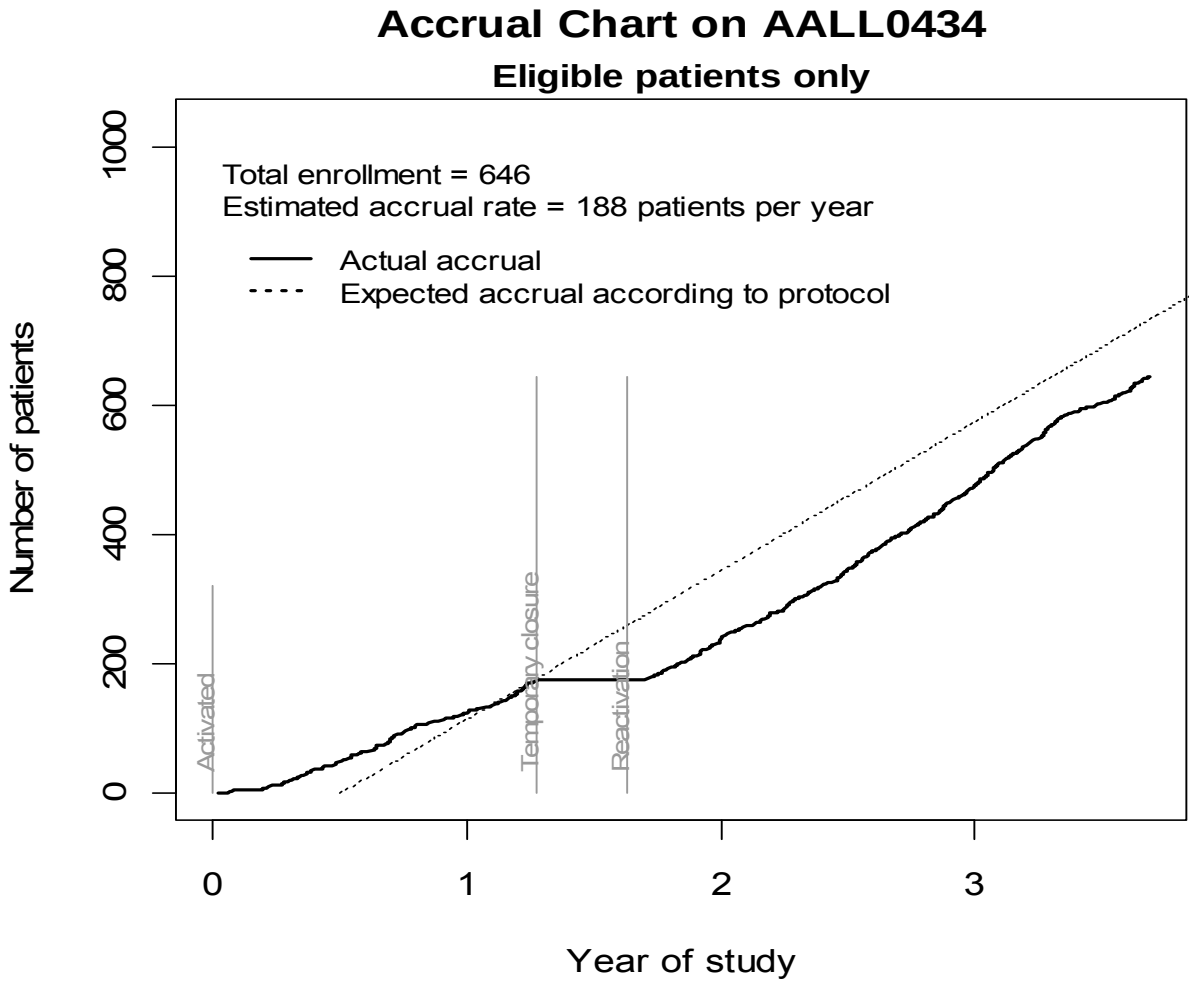
AALL0434 Accrual status

- Safety phase - completed (high risk only)
  - Presented at ASH 2010, Dr Winter, et al
- Efficacy phase - currently enrolling (intermediate and high risk)
- As of Feb 4, 2011
  - 565 of total 1380 subjects have been enrolled
  - 116 of 615 subjects have been randomized to Arranon assessment groups (chemotherapy +/- Arranon)
    - 102 High Risk, 14 Intermediate Risk

AALL0434 completion timelines

Milestone	Original timeline	Actual/current forecast
Arranon Approval date	N/A	28 Oct 2005
First patient enrolled	Apr 2006	Jan 2007
End of Safety phase	4Q2009	3Q2010
Complete Accrual	4Q2012	4Q2013
Complete 3-yr follow-up	4Q2015	4Q2016
Availability of study report	4Q2016	4Q2017

AALL0434 Accrual Rate[a]



[a]As of Sept. 2010

AALL0434 Summary

- Estimated date of the final study report: 4Q2017. Represents a delay of approx. one year from original estimate
- Most of this delay due to availability of final protocol
- The study is now recruiting according to plan and is expected to deliver a final study report as currently projected
- ***No further delays are currently anticipated***